REMARKS

In this Amendment, claims 2 and 8 are amended, claims 3-7 and 9-10 are canceled, and claims 11-13 are new. Therefore, after entry of this Amendment, claims 2, 8, and 11-13 are pending in this application.

Claim 2 is amended to indicate that the polypeptide is "isolated" for compliance with Section 101.

Claim 8 has been amended to further define the activity of the polypeptide. This amendment is supported by Examples 5, 6, and 7 of the specification.

Claim 8 has also been placed in independent form.

New claims 11 and 13 are supported by the original claims.

New claim 12 recites a further step (4) of the screening method, which is supported by the specification at page 26, lines 10-23.

No new matter has been added, and therefore, entry of this Amendment is respectfully requested.

Initially, the withdrawal of the restriction between Group V and Group I is much appreciated.

I. Priority Claim

The Examiner is kindly requested to acknowledge the claim for foreign priority, and to indicate whether the certified copies of the priority documents have been received.

II. Response to Objections to the Specification and Claims

(1) At page 3 of the Office Action, the Examiner objects to the Abstract as containing two paragraphs.

A substitute Abstract has been resubmitted with this Amendment containing a single paragraph.

(2) At page 4 of the Office Action, the Examiner objects to claims 2, 9 and 10 (sic. 2, 8 and 9) because the Examiner prefers the language "amino acid sequence of SEQ ID NO: 2."

Claims 2 and 8 have been amended accordingly, and claim 9 has been canceled.

(3) At page 4 of the Action, claim 9 is objected to because "ostcoarthritis" should be "osteoarthritis."

While this appears to have resulted from a scanning error at the PTO, claim 9 has nevertheless been canceled.

(4) At page 4 of the Action, claims 8 and 9 are objected to because "95% or more of homology" is grammatically incorrect.

The word "of" has been removed in claim 8. Claim 9 has been canceled.

(5) At page 4 of the Action, claim 9 is objected to under 37 C.F.R. § 1.76(c) as being in improper form.

Claim 9 has been canceled.

Withdrawal of the objections to the specification and claims is respectfully requested.

III. Response to Claim Rejection Under 35 U.S.C. §101

At page 4 of the Office Action, claim 2 is rejected under 35 U.S.C. §101 as covering the recited polypeptide in its natural state. The Examiner states that the rejection may be overcome by amending the claims to recite "an isolated" polypeptide.

Claim 2 has been amended to recite an "isolated" polypeptide as suggested by the Examiner.

Withdrawal of this rejection is respectfully requested.

IV. Response to Claim Rejection Under 35 U.S.C. §112, Second Paragraph

At page 5 of the Office Action, claims 8 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that the activity being analyzed should be specified.

Claim 9 has been canceled.

Claim 8 (as well as new claim 10) recite the activity: "to produce reactive oxygen species (ROS)," "to accelerate expression of TNF-α," and/or "to accelerate expression of COX-2."

Withdrawal of this rejection is respectfully requested.

IV. Response to Claim Rejections Under 35 U.S.C. §112, First Paragraph

(1) At page 5 of the Office Action, claims 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as not complying with the written description requirement.

Specifically, the Examiner states that the specification does not teach all possible polypeptide sequences expressed in RA patients that have 95% or more homology with SEQ ID

NO:2, and does not teach any structure-function relationships that would indicate to one of ordinary skill in the art that Applicants were in possession of more sequences than SEQ ID NO: 2.

This rejection is respectfully traversed.

The specification discusses the homology of SEQ ID NO: 2 with other known polypeptides at the paragraph bridging pages 2 and 3 of the specification, as well as at the paragraph bridging pages 9 and 10. The Examiner is respectfully requested to consider the full disclosure of the present specification, which is sufficient to show that Applicants were in possession of the claimed genus.

Additionally, the Examiner's attention is respectfully directed to Example 14 of the "REVISED INTERIM WRITTEN DESCRIPTION GUIDELINES TRAINING MATERIALS" (pages 53-56 are attached hereto as available on the Patent Office web-site).

Specifically, Example 14 indicates that the written description requirement may be satisfied for a variant having at least 95% homology where: the central sequence is exemplified, variants are contemplated, procedures for making modifications are routine in the art, and an assay for detecting activity of the protein is described.

It is respectfully submitted that Example 14 of the Patent Office written description guidelines supports patentability of the present claims under Section 112. (See Examples 5-7 of the Specification, as well as pages 15-17).

(2) At page 6 of the Office Action, claims 8 and 9 are rejected under 35 U.S.C. §112, first paragraph, as not complying with the enablement requirement.

Specifically, the Examiner states that the specification teaches one of ordinary skill in the art how to make and use a method with a polypeptide that consists of SEQ ID NO:2, but does not teach how to make and use the method for homologs of SEQ ID NO:2.

This rejection is respectfully traversed.

The present specification provides ample guidance to practice the full invention without undue experimentation.

The specification discusses the homology of SEQ ID NO: 2 with other known polypeptides at the paragraph bridging pages 2 and 3 of the specification, as well as at the paragraph bridging pages 9 and 10. Thus, suitable modifications to SEQ ID NO: 2 within the scope of the claims can be reasonably predicted.

Further, the technique of mutagenesis itself was routine in the art as of the present Application's filing date. For example, the technique of mutagenesis was used in a routine manner in the following literature references (copies of which are attached to this Amendment).

(1) Porter et al., In vivo DNA-binding and oligomerization properties of the *Shigella flexneri* AraC-like transcriptional regulator VirF ***as identified by random and site-specific mutagenesis***, *Journal of Bacteriology* 184(2): 531-539 (January 2002).

(2) Buchanan et al., Functional complexity of the twin-arginine translocase TatC component ***revealed by site-directed mutagenesis***, *Molecular Microbiology*, 43(6):1457-1470 (March 2002).

(3) Mathieu et al., Comparison of the hamster and human adrenal P450c17 (17 α-hydroxylase/17,20-lyase) ***using site-directed mutagenesis*** and molecular modeling, *Journal of- Steroid Biochemistry and Molecular Biology,* 80(1): 99-107 (January 2002).

(4) Auvray et al., Study of substrate specificity of human aromatase ***by-site-directed mutagenesis***, *European Journal of Biochemistry* 269(5): 1393-1405 (March 2002).

(5) Ren et al., Identification of the active site of poly(A)-specific ribonuclease ***by site-directed mutagenesis*** and Fe2+-mediated cleavage, *Journal of Biological Chemistry* 277(8): 5982-5987 (February 22, 2002).

In addition, at the time of filing the present application, a kit for site-directed mutagenesis was available (i.e. Quickchange™ site-directed mutagenesis kit available from Stratagene).

Accordingly, it is respectfully submitted that the present claims can be practiced with only routine experimentation on the basis of the present specification.

Withdrawal of these rejections is respectfully requested.

V. Response to Rejection Under 35 U.S.C. §102(b)

At page 8 of the Office Action, claim 2 is rejected under 35 U.S.C. §102(b) as being anticipated by Banfi, et al. (GenBank accession No. AF 166328), and *Science*, 287(5450): 138-142 (Jan. 7 2000).

Specifically, the Examiner contends that Banfi et al. disclose the sequence of a human polypeptide that is 100% homologous to SEQ ID NO:2 of claim 2.

This rejection is respectfully traversed.

As described in the specification, there is one amino acid difference between the sequence of the reference (AF166328) and the sequence of SEQ ID NO:2. Specifically, amino acid 173 of SEQ ID NO: 2 is Valine, which is Isoleucine in AF166328.

Accordingly, SEQ ID NO:2 is novel.

Withdrawal of this rejection is respectfully requested.

VI. Response to Rejection Under 35 U.S.C. §103(a)

At page 9 of the Office Action, claims 8 and 9 are rejected under 35 U.S.C. §103(a) as being obvious over Banfi et al., in view of Ostrakhovitch et al., *Biochem Pharmacol.* 62(6): 743-6 (Sept. 15, 2001).

Specifically, the Examiner states that Banfi et al. teach a polypeptide consisting of SEQ ID NO:2, and that the polypeptide may play a role in cellular defense against acidic stress.

The Examiner acknowledges that Banfi et al. do not teach a method of screening for a substance that inhibits NADPH oxidase, and do not disclose any inhibitors of NADPH oxidase that might be used to treat RA.

However, the Examiner asserts that Ostrakhovitch et al. teach oxidative stress in RA leukocytes and that the oxidative stress develops due to the activation of NADPH oxidase followed by accumulation of reactive oxygen species (ROS).

The Examiner further asserts that Ostrakhovitch et al. teach a method for identifying compounds that inhibit oxidative stress and one of those compounds was rutin, which is effective against oxidative stress due to RA.

Thus the Examiner concludes that one of ordinary skill in the art wanting to find compounds that inhibit oxidative stress and that are effective against RA would readily use the polypeptide of Banfi et al. in the method of Ostrakhovitch et al., in order to achieve the method of claims 8 and 9.

Reconsideration of this rejection is respectfully requested because the references do not provide a motivation to combine the respective teachings.

First, oxidative stress is based on a force to withdraw electrons, i.e., oxidation. On the other hand, acidic stress is based on a high concentration of hydrogen ions, i.e., strong acid. Thus, acidic stress and oxidative stress are different.

Ostrakhovitch teaches oxidative stress of RA leukocytes, but does not teach acidic stress.

Meanwhile, Banfi et al. (Science) teach that a proton channel for excreting intracellular protons participates in a protective mechanism for acidic stress, but does not teach that the proton channel participates in oxidative stress.

Second, there are various types of NADPH oxidase families, these are expressed differently. For example, as described in Banfi (Science), NOH-IS and NOH-1L are expressed differently: NOH-1L was detected in colon, uterus, prostate, and Caco-2 cells; but NOH-1S was detected only in colon and Caco-2 cells. It was also suggested that NOH-1S is expressed in HL-60 and leukocytes.

As further evidence that NADPH oxidases are expressed in different tissues, Cheng et al., *Gene* 269: 131-140 (2001), a copy of which is submitted with this Amendment, teaches that gp91*phox* (an NADPH oxidase) and homologs thereof (Nox3, Nox4, Nox5) are expressed in different tissues.

Thus, NADPH oxidases are not mere equivalents.

Accordingly, one of ordinary skill in the art would not combine the respective teachings of Banfi et al. and Ostrahovitch et al.

Particularly with respect to claims 11 and 13, since SEQ ID NO: 2 differs from the sequence of the reference (AF166328) by an amino acid, new claim 11 and 13 are non-obvious.

Withdrawal of these rejections is therefore requested.

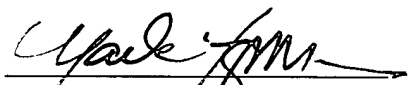
In summary, the present inventors discovered that NOX-lb, which is an NADPH oxidase, is expressed specifically in the synovial cells of RA patients as compared with the synovial cells of healthy individuals, thus leading to the present invention.

VII. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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